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This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

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INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
Dell'Orco	Philip	C	King of Prussia, Pennsylvania
Louvet	Ann	Marie	King of Prussia, Pennsylvania
Su	Qiaogong		King of Prussia, Pennsylvania
Wood	Jeffery	L	King of Prussia, Pennsylvania

TITLE OF THE INVENTION (280 characters max)

NOVEL COMPOUND, CORRESPONDING COMPOSITIONS, PREPARATION AND/OR TREATMENT METHODS

Correspondence Address:

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-4650
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-0939	Country	United States of America

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Respectfully submitted,
Signature:

Grace Hsu

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

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PU60518P

Novel Compound, Corresponding Compositions, Preparation and/or Treatment Methods

Field of the Invention

The present invention relates to novel crystalline topotecan hydrochloride forms, which may include crystalline topotecan hydrochloride polymorphs, hydrates, and/or solvates thereof, etc., corresponding pharmaceutical compositions, preparation methods, and/or uses in the treatment of certain disease states in mammals, in particular man.

The present invention further relates to a novel crystalline form of topotecan hydrochloride pentahydrate (i.e., a pentahydrate form of 10-[(dimethylamino) methyl]-4-ethyl-4,9-dihydroxy- 1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride or 9-dimethylaminomethyl-10-hydroxycamptothecin), corresponding pharmaceutical compositions, methods of preparation and/or use to treat anti-viral and/or cancer-related diseases.

Background of the Invention

A fundamental step to cellular DNA replication and transcription processes is associated with the separation of DNA helical strands.

DNA helical structure of eukaryotic cells dictate specific topological properties which may lead to problems that a cellular apparatus must resolve in order to use genetic material as a template for cellular replication processes. Eukaryotic DNA strands, organized into chromatin by chromosomal proteins, are constrained such that those strands cannot unwind without aid of topology altering enzymes. In light of this, it has long been recognized that advancement of a transcription or replication complex along a DNA helix would be facilitated by a swivel point that would relieve conformational torsional strain generated during such processes.

Topoisomerases are important enzyme components in cellular functions capable of altering DNA topology in eukaryotic cells and cell proliferation processes. Topoisomerases alter the linking number of DNA (i.e., equal to the number of times that a DNA strand winds in right handed helical axis direction) by catalyzing a three step process: the cleavage of one or both strands of DNA, the passage of a segment of DNA throught such break(s), and the resealing of the DNA break.

Two topoisomerase classes have been associated with eukaryotic cells: Type I Topoisomerase and Type II Topoisomerase. Both topoisomerases type I and type II play important roles in DNA replication, transcription, and recombination.

Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. Topoisomerase I relieves torsional strain in DNA by introducing reversible strand brakes. In particular, topoisomerase I binds to DNA, where it introduces a transient single-strand break to allow double helix unwinding, prevents religation of such single strand breaks, and subsequently reseals those breaks before dissociating from a DNA strand. Topoisomerase II, consisting of two identical subunits of molecular weight 170,000, transiently breaks both strands of the helix and passes another double-strand segment through the break.

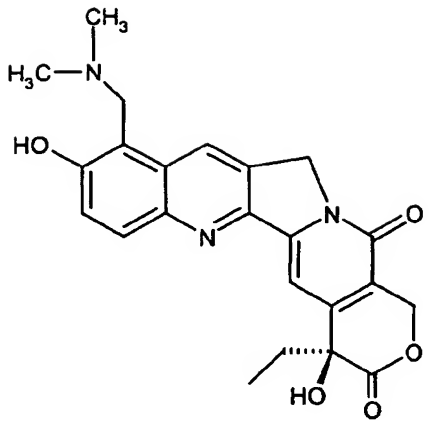
In general, inhibition of topoisomerase I has been the major target of oncologic, anti-neoplastic, anti-viral agents, etc. Inhibition of topoisomerase II is the major target of important commercial oncolytic agents (e.g., etoposide, doxorubicin and mitoxantrone) as well as other oncolytic agents still undergoing development.

An example of a class of DNA topoisomerase I inhibiting compounds include camptothecin and its corresponding analog or congener derivatives.

Camptothecin is a water-insoluble, cytotoxic alkaloid produced by Camptotheca accuminata trees indigenous to China and Nothapodytesfoetida trees indigenous to India. Camptothecins generally (such as topotecan) are discussed in Cancer Chemotherapy and Biotherapy (see, pp. 463-484; 2nd edition, eds. Bruce A. Chabner and Dan L. Longo, Lippincott-Raven Publishers, Philadelphia .Copyright 1996).

Examples of camptothecin analog derivatives, include topotecan, irinotecan, and 9-aminocamptothecin.

U.S. Pat. No. 5,004,758 to Boehm, et al., which is hereby incorporated by reference in its entirety, discloses Topotecan, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy- 1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride (also known as 9-dimethylaminomethyl-10-hydroxycamptothecin, etc.), as depicted by the following chemical structure:



(S) - Topotecan

Topotecan may exist in racemic, and/or respective (R) or (S) chiral configuration forms. Topotecan also is listed in The Merck Index (see 12th Ed., monograph no. 9687, Copyright 1996, Merck & Co., Inc.).

Generally, camptothecin and other toperisomerase I inhibiting congeners have not been shown to be attractive cytolytic agents due to undesirable characteristics (i.e., which include lack of clinical efficacy, unpredictable toxicity and unacceptable levels of dose-limiting toxicity, low aqueous solubility and poor shelf-life, etc.)

However, clinical tests have shown that topotecan demonstrates efficacy against several solid tumor cancers, particularly ovarian cancer, esophageal cancer, and non-small cell lung carcinoma in humans.

Therefore, there is a need for different crystalline topotecan hydrochloride forms (i.e., such as polymorphic, hydrate, and/or solvate forms of topotecan hydrochloride, such as crystalline topotecan hydrochloride pentahydrate forms), corresponding preparation methods, and/or pharmaceutical compositions, which when used as topoisomerase I inhibiting agents in treatment methods do not have undesirable characteristics as associated with camptothecin and other related topoisomerase I inhibiting congeners.

For example, novel crystalline topotecan hydrochloride polymorphic, hydrate and/or solvate forms, thereof (i.e., such as crystalline topotecan hydrochloride pentahydrate forms), corresponding pharmaceutical compositions, preparation

and/or treatment methods, may exhibit greater aqueous solubility, chemical stability, sustained or prolonged drug or absorption levels, exhibit greater clinical efficacy, predictable toxicity and achieve acceptable levels of dose-limiting toxicity, better shelf-life, better reproducibility in manufacturing and formulation, etc.

It has now been shown that such novel crystalline topotecan hydrochloride forms can be isolated in novel polymorphic forms, hydrates, and/or solvates thereof (i.e., such as crystalline topotecan hydrochloride pentahydrate forms), which also have the potential to improve the stability of pharmaceutical compositions and/or formulations containing the aforementioned crystalline forms.

The present invention is directed to overcoming these and other problems encountered in the art.

Summary of the Invention

In general, the present invention relates to crystalline topotecan hydrochloride forms (i.e., such as polymorphs, solvates, and/or hydrates thereof), corresponding compositions, methods of preparation and/or use thereof in the treatment of certain disease states in mammals, in particular man.

In particular, the present invention relates to a compound which is a crystalline topotecan hydrochloride pentahydrate, which is a pentahydrate form of 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy- 1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride, or 9-dimethylaminomethyl-10-hydroxycamptothecin.

The present invention relates to a pharmaceutical composition, which comprises a crystalline topotecan hydrochloride pentahydrate form and a pharmaceutically acceptable adjuvant, carrier and/or excipient.

The present invention relates to a process for preparing a crystalline topotecan hydrochloride polymorphic, solvate, and/or hydrate form thereof, wherein the process, which comprises the steps of: [a] forming an aqueous organic solvent solution mixture containing topotecan hydrochloride; and [b] recrystallizing and/or slurrying the topotecan hydrochloride from the aqueous organic solution mixture to form and/or to precipitate the crystalline topotecan hydrochloride polymorph, solvate,

and/or hydrate form thereof; and [c] collecting by filtration the product crystalline topotecan hydrochloride polymorph, solvate, and/or hydrate form thereof.

The present invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of a crystalline topotecan hydrochloride pentahydrate polymorph, solvate, and/or hydrate form thereof.

The present invention relates to a method of treating cancer which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition (i.e., which may include a crystalline topotecan hydrochloride pentahydrate polymorph, solvate, and/or hydrate form thereof).

Brief Description of the Figures

Figure 1 is an x-ray powder diffractogram for crystalline topotecan hydrochloride pentahydrate form depicting characteristic peaks substantially identified from the region 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ).

Detailed Description of the Invention

The present invention relates to novel crystalline topotecan hydrochloride forms (i.e., which may include crystalline topotecan hydrochloride polymorphs, hydrates, and/or solvates thereof), corresponding pharmaceutical compositions, preparation methods, and/or uses in the treatment of certain disease states in mammals, in particular man.

In particular, the present invention relates to a compound which is a crystalline topotecan hydrochloride pentahydrate (i.e., forms which may include polymorphs, solvates, and/or hydrates thereof).

The present invention relates to a pharmaceutical composition, which comprises a crystalline topotecan hydrochloride pentahydrate (i.e., forms which may include polymorphs, solvates, and/or hydrates thereof) and a pharmaceutically acceptable adjuvant, carrier and/or excipient.

The present invention relates to a process for preparing a crystalline topotecan hydrochloride form (i.e., such as a polymorph, solvate, and/or hydrate

thereof), where the process comprises the steps of: [a] forming an aqueous organic solvent solution mixture containing topotecan hydrochloride; and [b] recrystallizing and/or slurrying the topotecan hydrochloride from the aqueous organic solution mixture to form and/or to precipitate the crystalline topotecan hydrochloride polymorph, solvate, and/or hydrate form; and [c] collecting by filtration the product crystalline topotecan hydrochloride form.

The present invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of a crystalline topotecan hydrochloride pentahydrate (i.e., forms may include polymorphs, solvates, and/or hydrates thereof).

The present invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition (which includes a crystalline topotecan hydrochloride pentahydrate (i.e., forms may include polymorphs, solvates, and/or hydrates thereof).

All topotecan salt compound forms suitable for use in the present invention, which include starting materials (i.e., such as topotecan hydrochloride), intermediates or products, etc. are prepared as described herein, and/or by the application or adaptation of known methods, which may be methods used heretofore or described in the literature.

For example, U.S. Pat. No. 5,004,758 to Boehm et al. discloses water soluble camptothecin analogs, which includes topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin), preferably (S)-topotecan, most preferably as the hydrochloride salt, which is hereby incorporated by reference in its entirety.

U.S. Patent Nos. 5,734,056 to Burk et al. discloses water soluble camptothecin compound analogs (which include topotecan), a preparation process for such analogs and/or intermediates thereof, which is hereby incorporated by reference in its entirety.

U.S. Patent Nos. 5,674,872 to Johnson discloses a treatment method for ovarian cancer, which comprises administration of an effective amount of a compound of the water soluble camptothecin analog class, which may include topotecan, etc. which is hereby incorporated by reference in its entirety.

U.S. Patent No. 5,756,512 to Johnson discloses a treatment method for non-small lung carcinoma, which comprises administration of an effective amount of a compound of the water soluble camptothecin analog class, which may include topotecan, which is hereby incorporated by reference in its entirety.

U.S. Patent No. 5,633,016 to Johnson discloses combination chemotherapy related to use of pharmaceutical compositions comprised of a camptothecin analog class compound (i.e., including topotecan) and a platinum coordination compound and a pharmaceutically acceptable carriers or diluents, and tumor cell growth inhibition methods administrating the aforementioned compositions, which may include topotecan, which is hereby incorporated by reference in its entirety.

U.S. Patent No. 6,582,689 to Johnson discloses compositions, which comprise potentiators, an interferon-gamma-inducing factor (IGIF; such as IL-18), in combination with a chemotherapeutic agent (which may include topotecan), processes for making such compositions, the use of such compositions compositions to inhibit the growth of tumors or cancerous cells, and/or for prevention and/or treatment of cancer in mammals, which is hereby incorporated by reference in its entirety.

U.S. Patent No. 5,155,225 to Fortunak et al. generally discloses methods for making pyrano[3',4':6,7]indolizino-[1,2-B]quinolinones, which is hereby incorporated by reference in its entirety.

U.S. Patent Nos. 5,405,963, 5,468,859 to Fortunak et al., U.S. Patent No. 5,541, 329, 5,700,939 to Fortunak, U.S. Patent Nos. 5,663,177, 5,670,500 to Berges et al., each disclose respectively general processes for asymmetric total synthesis of camptothecin analogues and/or corresponding compound intermediates, pharmaceutical compositions, methods of making and/or use of analogs, etc. each respectively which are incorporated hereby by reference in its entirety.

One aspect of the present invention relates to novel crystalline topotecan hydrochloride (i.e., forms may include different polymorphs, solvates, and/or hydrates thereof).

In light of the foregoing, it is recognized that crystalline topotecan hydrochloride forms, may exist as stereoisomers, regioisomers, or diastereomers, etc. (e.g., which may contain one or more asymmetric carbon atoms). For example,

topotecan hydrochloride (i.e., defined as 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy- 1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride or 9-dimethylaminomethyl-10-hydroxycamptothecin), may exist in respective separate optically active forms, i.e., as either the R(+) enantiomer form or in the S(-) enantiomer form, and/or as racemic mixture of R(+) and S(-) enantiomers. All of such individual compounds, isomers, and mixtures thereof are included within the scope of the present invention.

According to one aspect of the present invention, novel crystalline topotecan hydrochloride forms, may exist as different polymorphs, hydrates, and/or solvates thereof, etc.

In light of this, crystalline topotecan hydrochloride forms of the present invention (i.e., which may include different polymorphs, solvates, and/or hydrates thereof) may exhibit characteristic polymorphism. As conventionally understood in the art, polymorphism is defined as an ability of a compound to crystallize as more than one distinct crystalline or "polymorphic" species. A polymorph is defined as a solid crystalline phase of a compound with at least two different arrangements or polymorphic forms of that compound molecule in the solid state.

Polymorphic forms of any given compound, including those of the present invention, are defined by the same chemical formula and/or composition and are as distinct in chemical structure as crystalline structures of two different chemical compounds. Such compounds may differ in packing, geometrical arrangement of respective crystalline lattices, etc.

In light of the foregoing, chemical and/or physical properties or characteristics vary with each distinct polymorphic form, which may include variations in solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, stability, etc.

Solvates and/or hydrates of topotecan hydrochloride of the present invention also may be formed when solvent molecules are incorporated into the crystalline lattice structure of the compound molecule during the crystallization process. For example, solvate forms of the present invention may incorporate nonaqueous solvents such as methanol, ethanol, propanol, isopropanol, DMSO, acetic acid,

ethanolamine, and the like. Hydrate forms are solvate forms, which incorporate water as a solvent into a crystalline lattice.

The present invention also relates to crystalline topotecan hydrochloride pentahydrates in various polymorphic, solvate, and/or hydrate forms thereof, each of which respectively, has a crystalline lattice structure that may incorporate crystal water bound lattice molecules and/or labile channel water molecules.

In one embodiment, the present invention relates to a crystalline topotecan hydrochloride pentahydrate form, which may include, but is not limited to different pentahydrate forms of the (S)-10-[(dimethylamino) methyl]-4-ethyl-4,9-dihydroxy- 1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride (also known as pentahydrates of (S)-9-dimethylaminomethyl-10-hydroxycamptothecin).

The crystalline topotecan hydrochloride pentahydrate compounds of the present invention may have a water content range between from about ≥ 10% w/w% to about ≤ 17 w/w%. The water content associated with the crystalline topotecan hydrochloride pentahydrate may also be in a range of about 3.5 wt% to about 20 wt%, with a preferred water content in a range of about 10.5 wt% to about 16.5 wt%.

Preferably crystalline topotecan hydrochloride pentahydrate of the present invention has a crystalline lattice structure, which may incorporate at least three crystal lattice bound water molecules therein. Crystalline topotecan hydrochloride pentahydrate may also include a crystalline lattice structure, which incorporates at least two coordinatively bound labile channel water molecules.

In accordance with the present invention, it has been unexpectedly found that topotecan hydrochloride can be isolated readily as novel crystalline forms (i.e., which may include different polymorphs, solvates, and/or hydrates thereof) which display greater uniformity, reproducibility in manufacture, stability on isolation, drying, and further processing, appearance, and bioavailability which may result in characteristic physical, biological, pharmacological and/or chemical stability changes.

Thus according to the instant invention, crystalline topotecan hydrochloride, (i.e., such as crystalline topotecan hydrochloride pentahydrate forms), which include polymorphic, solvate and/or hydrate forms thereof, may be distinguished from each other using different characterization or identification techniques.

For example, conventional organic chemistry identification techniques may be used to differentiate between different polymorphic phases present. Such identification techniques may include, but are not limited to: Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (NMR) (i.e., such as Proton Magnetic Resonance (^{1}H NMR), ^{13}C Nuclear Magnetic Resonance (NMR), ^{31}P Nuclear Magnetic Resonance (NMR)), Electron Microscopy, X-Ray Powder Diffraction, Optical Crystallography, Differential Scanning Calorimetry (DSC), Differential Thermal Analysis, Dilatometry, etc.

As indicated above, the present invention relates to a compound which is represented as different crystalline topotecan hydrochloride pentahydrate forms (i.e., which may include polymorphs, solvates, and/or hydrates thereof).

In accordance with the present invention, crystalline topotecan hydrochloride polymorphs, solvates, and/or hydrates thereof may be isolated in different and distinct crystalline forms, such as crystalline Topotecan pentahydrate forms of the present invention.

Specificallly, crystalline topotecan hydrochloride forms are shown substantially by the x-ray diffraction pattern data as depicted in Figure 1.

For example, crystalline topotecan hydrochloride pentahydrate (see, Example 1, which is identified by an x-ray diffraction pattern as shown substantially in Figure 1, which depicts characteristic peaks substantially identified from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 4.5 ± 0.1 (2θ), 6.4 ± 0.1 (2θ), 7.1 ± 0.1 (2θ), 9.0 ± 0.1 (2θ), 10.1 ± 0.1 (2θ), 11.5 ± 0.1 (2θ), 12.6 ± 0.1 (2θ), 13.1 ± 0.1 (2θ), 14.1 ± 0.1 (2θ), 15.5 ± 0.1 (2θ), 17.9 ± 0.1 (2θ), 18.7 ± 0.1 (2θ), 20.0 ± 0.1 (2θ), 20.3 ± 0.1 (2θ), 21.1 ± 0.1 (2θ), 21.8 ± 0.1 (2θ), 23.0 ± 0.1 (2θ), 24.8 ± 0.1 (2θ), 25.6 ± 0.1 (2θ), 26.6 ± 0.1 (2θ), 27.2 ± 0.1 (2θ), and 28.9 ± 0.1 (2θ).

In addition, the present invention relates to a process for preparing crystalline topotecan hydrochloride forms.

In accordance with the present invention, different polymorphs, solvates, and/or hydrates may be produced, for example, by changing or adjusting the reaction conditions, such as reagents, organic solvents, aqueous solvents, temperature, etc., used in making, forming, precipitating, etc. such aforementioned compound forms. In addition, a polymorph, solvate, and/or hydrate of the present

invention may spontaneously convert to another polymorph when subject to certain and specific chemical, physical, thermal condition changes, etc.

In particular, the present invention relates to a process for preparing a crystalline topotecan hydrochloride polymorph, solvate, and/or hydrate thereof, where the process comprises the steps of: [a] forming an aqueous organic solvent solution mixture containing topotecan hydrochloride; and [b] recrystallizing and/or slurrying the topotecan hydrochloride from the aqueous organic solution mixture to form and/or to precipitate the crystalline topotecan hydrochloride polymorph, solvate, and/or hydrate form; and [c] collecting by filtration the product crystalline topotecan hydrochloride polymorph, solvate, and/or hydrate thereof.

Further, the present invention relates to a process for preparing a crystalline topotecan hydrochloride pentahydrate polymorph, solvate, and/or hydrate thereof, where the process comprises the steps of: [a] forming an aqueous organic solvent solution mixture containing topotecan hydrochloride; and [b] recrystallizing and/or slurrying the topotecan hydrochloride from the aqueous organic solution mixture to form and/or to precipitate the crystalline topotecan hydrochloride pentahydrate polymorph, solvate, and/or hydrate thereof; and [c] collecting by filtration the product crystalline topotecan hydrochloride pentahydrate polymorph, solvate, and/or hydrate thereof.

Suitable organic solvents for use processes of the present invention, which may be used to form aqueous organic solutions may include, but are not limited to, acetone, tetrahydrofuran, methanol, ethanol, n-propanol, isopropanol, acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, ethyl acetate, dichloromethane, and the like. Preferred solvents, may include, but are not limited to non-hydroxylic solvents that are miscible with water, such as acetone, tetrahydrofuran, or acetonitrile, and the like.

In a process of the present invention, the aforementioned aqueous organic solvent solution mixture may further comprise a mineral acid (i.e., such as hydrochloride acid solutions in various concentrations), which aids in stabilization of crystalline topotecan hydrochloride products of the present invention (i.e., which may include polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms).

For example, suitable crystalline topotecan hydrochloride polymorphs, solvates and/or hydrates, thereof the present invention may be prepared by either recrystallizing and/or slurrying topotecan hydrochloride in a single solvent or a mixture containing only organic solvents or an aqueous organic solvent mixture, such as acetone and a hydrochloride solution in various concentrations.

With respect to a process of the present invention, the recrystallizing or crystallizing step utilizing topotecan hydrochloride to form crystalline topotecan hydrochloride forms (i.e., which may include polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate), may be initiated by seeding an aqueous organic solution containing the topotecan hydrochloride material with crystals of a desired polymorph, solvate, and/or hydrate form, though seeding is not an essential to the formation of such desired polymorph, solvate, and/or hydrate forms.

With respect to step [b] in a process of the present invention, recrystallizing and/or slurrying topotecan hydrochloride may form and/or precipitate the product crystalline topotecan hydrochloride form, such as a crystalline topotecan hydrochloride pentahydrate form, which may have a water content in a range from about 3.5 wt% to about 20 wt%.

For recrystallization and/or slurrying processes indentified in step [b], an aqueous organic solvent solution mixture used in an aforementioned process of the present invention may have an organic solvent to water ratio from about 1.5 : 1 to about 8 : 1. A preferable range of an organic solvent to water ratio is from about 1.5 : 1 to about 3.1 : 1, more preferably about 2 : 1. Another preferable range of an organic solvent to water ratio from about 2 : 1 to about 8 : 1, more preferably about 8 : 1.

Such an aqueous organic solvent solution mixture may have a volume of organic solvent to topotecan hydrochloride ratio is from about 7 : 1 to about 13 : 1. A preferable range of an aqueous organic solvent solution mixture may have a volume of organic solvent to topotecan hydrochloride ratio is from about 10.6 : 1 to about 13 : 1, more preferably 12 : 1. Another preferable range of an aqueous organic solvent solution mixture may have a volume of organic solvent to topotecan hydrochloride ratio is from about 7 : 1 to about 12 : 1, more preferably 12 : 1.

Suitable crystalline topotecan hydrochloride forms, such as crystalline topotecan hydrochloride pentahydrate forms (i.e., respectively may include polymorphs, solvates, and/or hydrates thereof) formed via an aforementioned process of the present invention may have a crystalline lattice structure, which may incorporate at least three bound water molecules therein and/or may incorporate at least two coordinating labile water molecules.

Importantly, the chemical and/or physical properties of crystalline topotecan hydrochloride forms described herein (i.e., which include different polymorphs, solvates and/or hydrates thereof, etc., such as crystalline topotecan hydrochloride pentahydrate forms) may be particularly suitable for inclusion in medicinal agents, pharmaceutical compositions, etc.

In light of this, the present invention relates to a pharmaceutical composition, which may include a crystalline topotecan hydrochloride polymorph, solvate and/or hydrate (i.e., such as various crystalline topotecan hydrochloride pentahydrate forms), and a pharmaceutically acceptable adjuvants, carriers, diluents, and/or excipients.

In addition, if desired, a crystalline topotecan hydrochloride form (which may include a polymorph, solvate and/or hydrate thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions of the present invention may be combined with other active ingredients and pharmaceutically acceptable adjuvants, carriers, diluents, and/or excipients thereof.

For example, crystalline topotecan hydrochloride forms (i.e., such as polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) of the present invention may be used in conjunction with organometallic coordination compounds (e.g., such as platinum compounds, which may include, but are not limited to cisplatin, carboplatin and the like. etc.) in combination therapies for treatment of various diseases, such as inhibition of cancer related, anti-neoplastic tumors, etc.

The crystalline topotecan hydrochloride forms (i.e., such as polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or corresponding pharmaceutical compositions prepared according to the present invention may be used to treat warm blooded animals, such

as mammals, which include humans.

For example, crystalline topotecan hydrochloride forms (i.e., which include polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions of the present invention have both a human and a veterinary utility that is acceptable for the intended aforementioned compounds and/or corresponding pharmaceutical composition end use. If a veterinary use is intended, the carrier may be a liquid, or spray, or may be formulated in a solid, non-degradeable or degradeable form for insertion in the rumen. Selected adjuvants, carriers, diluents, and/or excipients thereof, etc. may be employed to prepare compositions acceptable or adaptable for human use.

In general, pharmaceutical compositions of the present invention are prepared using conventional art known materials and techniques, which may include, but are not limited to mixing, blending and the like.

Suitable adjuvants, carriers, diluents, and/or excipients contemplated for use in pharmaceutical compositions of the present invention may be include those known in the pharmaceutical formulary arts. For example, a reference to useful materials may be found in well-known pharmaceutical formulary compilation text books, such as Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa).

Moreover, a wide variety of pharmaceutical forms may be employed for use with the present invention.

In accordance with the present invention, crystalline topotecan hydrochloride forms (i.e., such as polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical composition also may also include, but are not limited to, suitable adjuvants, carriers, excipients, or stabilizers and the like.

In light of the foregoing, such adjuvants, carriers, diluents, and/or excipients, etc. used in forming pharmaceutical compositions of the present invention may be either a solid (i.e., such as, tablets, capsules, powders, etc.) or liquid form (i.e., such as solutions, suspensions, or emulsions, etc.)

Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge.

The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram.

If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable solution Or suspension in an ampule or vial or nonaqueous liquid suspension. To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of the compound of Formula I is dissolved in an aqueous solution of an organic or inorganic acid or base. If a soluble salt form is not available, the compound of Formula I may be dissolved in a suitable co-solvent or combinations thereof. Examples of such suitable co-solvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume.

Moreover, if a desired pharmaceutical composition is employed in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents include: for aqueous systems, water; for non-aqueous systems: ethanol, glycerin, propylene glycol, olive oil, corn oil, cottonseed oil, peanut oil, sesame oil, liquid paraffins, and mixtures thereof with water; for solid systems: lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, kaolin and mannitol; and for aerosol systems: dichlorodifluoromethane, chlorotrifluoroethane and compressed carbon dioxide.

Also, pharmaceutical compositions of the present invention may include other ingredients such as stabilizers, antioxidants, liposomes, preservatives, lubricants, suspending agents, viscosity modifiers and the like, provided that the additional ingredients do not have a detrimental effect on the therapeutic action of the instant compositions. Similarly, the adjuvant, carrier, diluent and/or excipient may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

As indicated, lipid formed liposomes are pharmaceutical compositional components that may be used in the present invention. Such lipid formed liposomes when combined with crystalline topotecan hydrochloride polymorphs, solvates and/or hydrates (i.e., such as crystalline topotecan hydrochloride pentahydrate) form relatively stable vesicles (where the lipid-containing membrane structures enclose an

aqueous interior).

A variety of lipids are known in the art which may be used to generate such liposomes. Generally single-layered liposomes have one membrane and are defined as "unilamellar"). Multilayer liposomes are referred to as "multilamellar." Suitable lipids for use in the present invention, include, but are not limited to, neutral and negatively charged phospholipids or sphingolipids and sterols, such as cholesterol.

U.S. Pat. No. 5,814,335 to Webb et al. discloses a liposome type, known as sphingosomes, also which is suitable for use pharmaceutical compositions of the present invention, is hereby incorporated by reference in its entirety. Specifically, liposome compositions for use in the present invention, may include, but are not limited to, those which comprise various ratios of sphingomyelin and cholesterol. For example, a ratio of sphingomyelin to cholesterol in the liposome composition may vary, but generally may be in a range of from about 75/25 mol %/mol % sphingomyelin/ cholesterol to about 30/50 mol %/mol % sphingomyelin/cholesterol, more preferably about 70/30 mol %/mol % sphingomyelin/cholesterol to about 40/45 mol %/mol % sphingomyelin/ cholesterol, and even more preferably about 55/45 mol %/mol % sphingomyelin/ cholesterol. Other lipids also may be included in such liposome containing compositions of the present invention as may be necessary, such as to prevent lipid oxidation or to attach ligands onto the liposome surface. Generally, if lipids are included, the other inclusion of such lipids will result in a decrease in the sphingomyelin/cholesterol ratio.

In addition, solubility of various crystalline topotecan hydrochloride forms, (i.e., which include different polymorphs, solvates and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms), as those described herein may facilitate provision or development of a dosage form from which the drug substance becomes better available for bioabsorption. As a result, it may be possible to develop stable controlled release dosage forms, which contain such crystalline topotecan hydrochloride polymorphs, solvates and/or hydrates thereof and/or corresponding pharmaceutical compositions of the present invention, for once-per-day dosage, controlled or delayed release or pulsatile release regiments, etc., to optimize therapy by matching pharmacokinetic performance with pharmacodynamic requirements.

Typically, a pharmaceutical composition of the present invention may contain crystalline topotecan hydrochloride forms, (i.e., which include different polymorphs, solvates and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) of the present invention.

In one embodiment of the present invention, a pharmaceutical composition may comprise various forms of crystalline topotecan hydrochloride pentahydrate, (i.e., which include different polymorphs, solvates and/or hydrates thereof) together with the adjuvants, carriers, diluents, and/or excipients, etc.

In accordance with the present invention, crystalline topotecan hydrochloride forms, such as crystalline topotecan hydrochloride pentahydrate forms (i.e., which includes polymorphs, solvates, and/or hydrates thereof) and/or pharmaceutical compositions of the present invention can be useful in treatment methods for a variety of diseases and conditions, which may include, but are not limited to anti-viral, anti-neoplastic activity, various cancers, etc. For example, anti-neoplastic activity may include treatment of solid tumor types (i.e., which may include, but are not limited to endometrial tumors, neuroblastomas, and the like, etc.) and non-solid tumor types (i.e., which may include, but are not limited to myelodysplastic syndrome, acute myelogenous leukemia, chronic myelomonocytic leukemia, and the like, etc.). Various cancers treatable by compounds, pharmaceutical compositions and/or methods of the present invention, may include, but are not limited to ovarian cancer, endometrial cancer, esophageal cancer, and small and non-small cell lung cancer, cevical cancer, colorectal cancer, glioma in mammals, such as humans.

In light of the foregoing, the present invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of a crystalline topotecan hydrochloride pentahydrate form (i.e., which includes polymorphs, solvates, and/or hydrates thereof).

Further, the present invention also relates to a method of treating cancer which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition (which includes a crystalline topotecan hydrochloride pentahydrate, i.e., which includes polymorphs, solvates, and/or hydrates thereof).

Crystalline topotecan hydrochloride forms, (i.e., which include different polymorphs, solvates and/or hydrates thereof, such as crystalline topotecan

hydrochloride pentahydrate forms) and/or pharmaceutical compositions within the scope of this invention include all compounds, pharmaceutical compositions, and corresponding treatment methods, wherein the aforementioned compounds of the present invention may be contained in an amount effective to achieve its intended purpose.

While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art.

Specifically, treatment regimens for the administration of the compounds and/or compositions of the present invention also may be determined readily by those with ordinary skill in art.

Moreover, the quantity of the crystalline topotecan hydrochloride forms, (i.e., which include different polymorphs, solvates and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions within the present invention as administered will vary over a wide range based upon each individual patient, such that a unit dosage provided is in an effective amount based upon patient body weight or surface area, administration mode per day to achieve the desired effect, etc. (and may be in any effective amount to achieve the desired effect).

In accordance with the present invention, the term "effective amount" means that amount of a crystalline topotecan hydrochloride form (i.e., which includes polymorphs, solvates and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or corresponding pharmaceutical composition, upon administration to a mammal (such as a human being), in need thereof provides a clinically desirable result in the treatment of various diseases i.e., such as virally-related and/or cancer diseases (i.e., the latter of which may include anti-neoplastic treatment, which includes, but not limited to, tumor cell growth inhibition, remission, or cure, etc.).

In light of this, it will be appreciated that the actual preferred course of therapy will vary according to, inter alia, the mode of administration, the particular formulation of a compound of the water soluble camptothecin analog class form (i.e., which include crystalline topotecan hydrochloride and/or polymorphs, solvates and/or

hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) being utilized, the mode of administration and the particular host being treated.

An optimal therapy course for a given set of conditions may be ascertained by those skilled in the art using conventional course of therapy determination tests in view of the information set out herein and a examples set forth in U.S. Pat. No. 5,004,758 to Boehm et al. and in U.S. Pat. No. 5,633,016 to Johnson, respectively each of which is incorporated hereby by reference in its entirety.

Further, it will be appreciated that the actual preferred dosages of the compound used in the compositions and methods of treatment of the present invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, such as host and tumor type being treated, etc.

Moreover, optimal dosages for a specific pathological condition in a particular patient may ascertained by those of ordinary skill in the art, such as in the anti-viral or anti-neoplastic arts, using conventional dosage determination tests in view of the experimental data. In accordance with the present invention, components of each pharmaceutical composition and corresponding adjuvants, carriers, excipients, diluent etc., will depend upon the treatment effected and/or intended route of administration.

Thus, crystalline topotecan hydrochloride forms, i.e., which includes polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions of the present invention may be administered by intravenous and intramuscular injection, parenterally, topically, orally, or by inhalation.

The percentage of the crystalline topotecan hydrochloride forms, i.e., which includes polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) in pharmaceutical compositions of the present invention may be varied for a desired amount of active compound in such therapeutically useful compositions such that a suitable dosage will be obtained.

The crystalline topotecan hydrochloride forms (i.e., which includes polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions of the

present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipients.

Such adjuvants, carriers, diluents, and/or excipients, include, but are not limited to sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable carrier, including adjuvants, excipients or stabilizers, etc. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Suitable oils for use in the present invention may include, but are not limited to petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil, and the like.

In general, liquid carriers, particularly for injectable solutions, may include, but are not limited to, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, and the like.

The pharmaceutical forms of the present invention suitable for injectable use, may include, but are not limited to, sterile aqueous solutions or dispersions and sterile powders for extemporaneous preparation of sterile injectable solutions or dispersions and the like. In all cases, each form should be sterile and be fluid to the extent that easy syringability exists. Such forms should be stable under conditions of manufacture and storage, which should be preserved against contaminating action of microorganisms, such as bacteria and fungi. For example, a carrier may be a solvent or dispersion medium which may include, but are not limited to water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), vegetable oils, suitable mixtures thereof, and the like.

For parenteral administration, a pharmaceutical composition of the present invention may include, but is not limited to be in the form of a sterile injectable liquid, such as an ampule or an aqueous or nonaqueous liquid suspension, and the like. Suitable solutions or suspensions of active compounds of the present invention may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Suitable dispersions also be prepared in, but not limited to glycerol, liquid polyethylene glycols, and oil mixtures thereof, and the like.

For parenteral administration of a compound of the water soluble camptothecin analog class (which include crystalline topotecan hydrochloride polymorph, solvate and/or hydrate forms, such as crystalline topotecan hydrochloride pentahydrate forms) a course of therapy generally employed is from about 0.5 mg/m^2 to about 25.0 mg/m^2 of body surface area per day for about one day to about five consecutive days. More preferably, the course of therapy employed for a patient is from about 1.0 mg/m^2 to about 2.5 mg/m^2 of body surface area per day for about five consecutive days. Most preferably, the course of therapy employed is from about 1.5 mg/m^2 to about 2 mg/m^2 of body surface area per day for about five consecutive days. Preferably, the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval (from the date of initiation of therapy) depending upon the initial dosing schedule and the patient's recovery of normal tissues.

Most preferably, the course of parental therapy continues to be repeated based on tumor response in cancer related diseases. Preferably, the parenteral administration will be by short (e.g., 30 minute) or prolonged (e.g., 24 hour) intravenous infusion. More preferably, compounds and/or pharmaceutical compositions of the present invention (i.e., such as crystalline topotecan hydrochloride in different forms, salts, polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate) will be administered by a 30 minute intravenous infusion. For continuous intravenous administration, the dose generally employed is about 0.5 mg/m^2/day for 5 days to 21 days.

For topical administration, a compound and/or pharmaceutical composition of the present invention may include, but is not limited to be in a form of a cream, ointment, liniment, lotion, paste, spray or drops suitable for administration to the skin, eye, ear, nose or genitalia and the like.

For oral administration, a compound and/or pharmaceutical composition of the present invention may include, but is not limited to be in the form of a tablet, capsule, powder, pellet, troche, lozenge, syrup, suspension, elixir, liquid, or emulsion and/or other solid unit dosage forms as conventionally known in the art and the like. For example, active compounds and/or pharmaceutical compositions of the present invention may be orally administered with an inert diluent, an assimilable edible

carrier, enclosed in hard or soft-shell capsules, compressed into tablets, and/or incorporated directly with food, etc.

A solid form suitable for use in the present invention may include, but is not limited to a capsule (i.e., such as an ordinary gelatin type containing compounds of the present invention and a carrier), lubricants, inert fillers (i.e., such as, lactose, sucrose, or cornstarch, etc.) and the like, etc. When the dosage unit form used is a capsule, it also may contain a liquid carrier (i.e., such as a fatty oil), etc.

In another embodiment, these crystalline topotecan hydrochloride forms (i.e., which includes polymorphs, solvates, and/or hydrates thereof, such as crystalline topotecan hydrochloride pentahydrate forms) and/or pharmaceutical compositions may be tableted with conventional tablet bases, which may include, but are not limited to lactose, sucrose, or cornstarch and the like, in combination with binders (i.e., such as acacia, gum, tragacanth, cornstarch, or gelatin, etc.), excipients (i.e., such as dicalcium phosphate), disintegrating agents (i.e., such as cornstarch, potato starch, or alginic acid), lubricants, (i.e., such as stearic acid, magnesium stearate, etc.); and a sweetening agent (i.e., such as sucrose, lactose, or saccharin, etc.). Various other materials may be present as coatings or to modify physical forms of each dosage unit associated with the present invention. For instance, tablets may be coated with materials, which may include, but are not limited to shellac and/or, sugar, a syrup (i.e., which may include, but is not limited to an active ingredient, a sweetening agent (i.e., such as sucrose), preservatives (i.e., such as methyl and propylparabens), a dye, and flavorings (i.e., such as cherry or orange flavors), and the like.

For oral administration of a compound of the water soluble camptothecin analog class, the course of therapy generally employed is from about 1.0 mg/m^2 to about 150.0 mg/m^2 of body surface area per day for about one to five consecutive days with courses of treatment repeated at appropriate intervals. More preferably, the course of therapy employed is from about 1.5 mg/m^2 to about 5.0 mg/m^2 of body surface area per day for about five consecutive days. Preferably, the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval (from the date of initiation of therapy) depending upon the initial dosing

schedule and the patient's recovery of normal tissues. Most preferably, the course of therapy continues to be repeated based on tumor response.

The various references to journals, patents, and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

Examples

Example 1

Crystalline Topotecan Hydrochloride Pentahydrate Preparation

Topotecan hydrochloride (2.9 g) was suspended in a mixture of acetone (23.2 mL, 8 volumes) and 0.05 **N** HCl (11.6 mL, 4 volumes). The aforementioned reaction mixture was heated to 58°C to dissolve the solid topotecan hydrochloride. The reaction mixture solution was cooled and formed a topotecan hydrochloride slurry. The topotecan hydrochloride crystallized at 37 °C. The slurry was cooled further to room temperature whereupon the reaction product, crystalline topotecan hydrochloride pentahydrate form, was isolated by filtration and dried by conventional techniques.

It is to be understood that the present invention is not limited to the embodiments illustrated hereinabove. It will be apparent to those skilled in the art that various modifications may be made without departing from the spirit of the invention, such that the right is reserved to illustrated embodiments and all modifications coming within the scope of the following claims.

What is claimed is:

1. A compound which is a crystalline topotecan hydrochloride pentahydrate.

2. The compound according to claim 1, wherein the crystalline topotecan hydrochloride pentahydrate has a crystalline lattice structure which incorporates at least three crystal lattice bound water molecules therein.

3. The compound according to claim 1, wherein the crystalline topotecan hydrochloride pentahydrate has a crystalline lattice structure which incorporates at least two coordinatively labile channel water molecules.

4. The compound according to claim 1, wherein the crystalline topotecan hydrochloride pentahydrate has a water content range between from about ≥ 10% w/w% to about ≤ 17 w/w%.

5. The compound according to claim 1, wherein the crystalline topotecan hydrochloride pentahydrate has a water content in a range of about 3.5 wt% to about 20 wt%.

6. The compound according to claim 5, wherein the crystalline topotecan hydrochloride pentahydrate has a preferred water content in a range of about 10.5 wt% to about 16.5 wt%.

7. The compound according to claim 1, having an x-ray diffraction pattern as substantially shown in Figure 1.

8. The compound according to claim 7 having characteristic peaks substantially identified from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 4.5 ± 0.1 (2θ), 6.4 ± 0.1 (2θ), 7.1 ± 0.1 (2θ), 9.0 ± 0.1 (2θ), 10.1 ± 0.1 (2θ), 11.5 ± 0.1 (2θ), 12.6 ± 0.1 (2θ), 13.1 ± 0.1 (2θ), 14.1 ± 0.1 (2θ), 15.5 ± 0.1 (2θ),

17.9 ± 0.1 (2θ), 18.7 ± 0.1 (2θ), 20.0 ± 0.1 (2θ), 20.3 ± 0.1 (2θ), 21.1 ± 0.1 (2θ), 21.8 ± 0.1 (2θ), 23.0 ± 0.1 (2θ), 24.8 ± 0.1 (2θ), 25.6 ± 0.1 (2θ), 26.6 ± 0.1 (2θ), 27.2 ± 0.1 (2θ), and 28.9 ± 0.1 (2θ).

9. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, and/or excipient.

10. A process for preparing a crystalline topotecan hydrochloride form, wherein the process comprises steps of:

[a] forming an aqueous organic solvent solution mixture containing topotecan hydrochloride; and

[b] recrystallizing and/or slurrying the topotecan hydrochloride from the aqueous organic solution mixture to form and/or to precipitate a product crystalline topotecan hydrochloride form; and

[c] collecting by filtration the product crystalline topotecan hydrochloride form.

11. The process according to claim 10, wherein as in step [b] recrystallizing and/or slurrying the crystalline topotecan hydrochloride forms and/or precipitates the product crystalline topotecan hydrochloride form as crystalline topotecan hydrochloride pentahydrate.

12. The process according to claim 11, wherein the crystalline topotecan hydrochloride pentahydrate polymorph has a crystalline lattice structure which incorporates at least three bound water molecules therein.

13. The process according to claim 11, wherein the crystalline topotecan hydrochloride pentahydrate has a crystalline lattice structure which incorporates at least two coordinating labile or channel water molecules.

14. The process according to claim 11, wherein as in step [b] recrystallizing and/or slurrying the crystalline topotecan hydrochloride forms and/or precipitates a crystalline topotecan hydrochloride pentahydrate with a water content in a range from about 3.5 wt% to about 20 wt%.

15. The process according to claim 10, wherein the aqueous organic solvent solution mixture further comprises a mineral acid.

16. The process according to claim 10, wherein the step of recrystallizing or slurrying further comprises the aqueous organic solvent solution mixture to have an organic solvent to water ratio from about 1.5 : 1 to about 8 : 1.

17. The process according to claim 16, wherein the aqueous organic solvent solution mixture is formed from an organic solvent to water ratio preferably from about 1.5 : 1 to about 3.1 : 1.

18. The process according to claim 16, wherein the organic solvent to water ratio is most preferably from about 2 : 1.

19. The process according to claim 10, wherein the aqueous organic solvent solution mixture is formed from an organic solvent to water ratio preferably from about 2 : 1 to about 8 : 1.

20. The process according to claim 19, wherein the organic solvent to water ratio is most preferably from about 8 : 1.

21. The process according to claim 10, wherein the step of recrystallizing or slurrying further comprises the aqueous organic solvent solution mixture to have a volume of organic solvent to topotecan hydrochloride ratio from about 7 : 1 to about 13 : 1.

22. The process according to claim 21, wherein the volume of organic solvent to topotecan hydrochloride ratio is preferably in a ratio from about 10.6 : 1 to about 13 : 1.

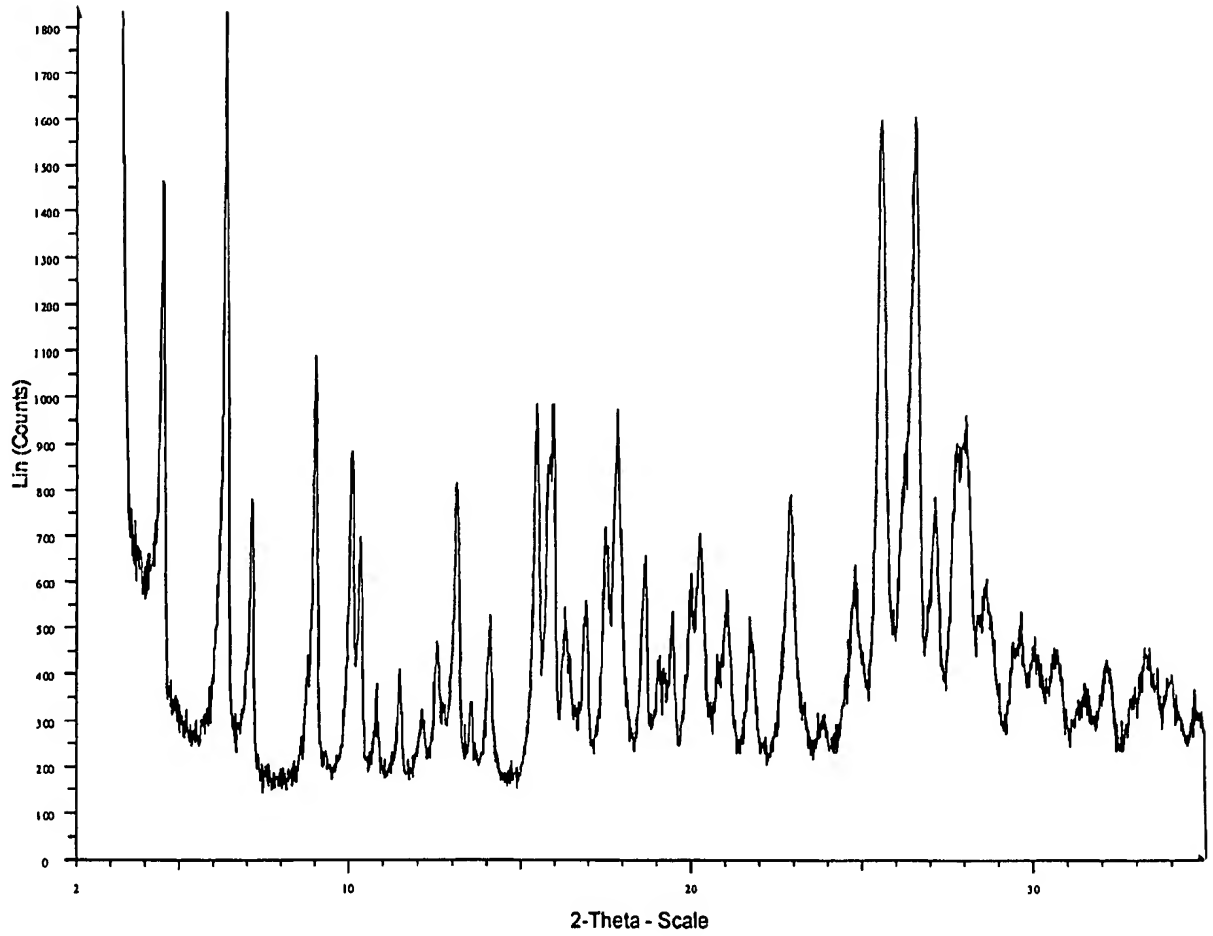
23. The process according to claim 22, wherein the volume of organic solvent to topotecan hydrochloride ratio is preferably in a ratio from about 7 : 1 to about 12 : 1.

24. A method of treating cancer which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

25. A method of treating cancer which comprises administering to a subject in need thereof an effective amount of the pharmaceutical composition according to claim 9.

ABSTRACT OF THE DISCLOSURE

The present invention relates to novel crystalline topotecan hydrochloride forms, which may include crystalline topotecan hydrochloride polymorphs, hydrates, and/or solvates thereof, etc., corresponding pharmaceutical compositions, preparation methods, and/or uses in the treatment of certain disease states in mammals, in particular man. The present invention also relates to a novel crystalline form of topotecan hydrochloride pentahydrate, which is a pentahydrate form of 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3', 4': 6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione monohydrochloride, (or 9-dimethylaminomethyl-10-hydroxycamptothecin, etc.), corresponding pharmaceutical compositions, methods preparation and/or use to treat anti-viral and/or cancer-related diseases, etc.


Lin (Counts)
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1600
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1800
2
10
20
30
2-Theta - Scale

Figure 1

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